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Association of Contemporary Sensitive Troponin I Levels at Baseline and Change at 1 Year With Long-Term Coronary Events Following Myocardial Infarction or Unstable Angina

Results From the LIPID Study (Long-Term Intervention With Pravastatin in Ischaemic Disease)

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Objectives This study sought to assess whether baseline and change in contemporary sensitive troponin I (TnI) levels predicts coronary heart disease (CHD) death and myocardial infarction (MI), and to determine the effects of pravastatin on TnI levels.

Background The role of troponins in predicting long-term outcomes in patients with stable CHD is not clearly defined.

Methods The LIPID (Long-Term Intervention With Pravastatin in Ischaemic Disease) study randomized patients with cholesterol levels of 155 to 271 mg/dl 3 to 36 months after MI or unstable angina to placebo or pravastatin 40 mg per day. TnI levels were measured at baseline and after 1 year in 7,863 patients. Median follow-up was 6 years. Change in TnI was defined as moving up or down 1 tertile or ≥50% change.

Results Baseline TnI tertiles were <0.006 ng/ml, 0.006 to <0.018 ng/ml, and ≥0.018 ng/ml. TnI levels were related to CHD death and MI after adjustment for 23 risk factors and treatment (≥0.018 ng/ml vs. <0.006 ng/ml hazard ratio [HR]: 1.64; 95% CI: 1.41 to 1.90; $p < 0.001$). TnI levels increased in 23.0%, were unchanged in 51.3%, and decreased in 25.7% of patients. Pravastatin decreased TnI levels by 0.003 ng/ml versus placebo ($p = 0.002$). In landmark analyses, increases in TnI levels were associated with increased numbers of CHD death and MI (HR: 1.31; 95% CI: 1.06 to 1.62) and decreases with decreased risk (HR: 0.90; 95% CI: 0.74 to 1.09; overall $p = 0.01$). Data were similar with 50% change criteria. Net reclassification improvement by adding TnI to the baseline model for CHD death and MI was 4.8% ($p = 0.01$).

Conclusions Baseline TnI levels and change at 1 year are independent predictors of CHD death and MI. TnI levels are strong predictors of risk, and change modifies risk. (J Am Coll Cardiol 2014;63:345–54) © 2014 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CHD = coronary heart disease
CVD = cardiovascular disease
hsCRP = high-sensitivity C-reactive protein
hsTnT = high-sensitivity troponinT
MI = myocardial infarction
TnI = troponin I

Cardiac troponin can be measured with high-sensitivity troponin assays in many individuals who are clinically well (1–3). In a recent large community-based study, detectable levels of hsTnT >0.003 ng/ml were found in 25% of the population and were associated with an increased risk of all-cause mortality (1). In patients with stable coronary heart disease (CHD) and preserved left ventricular ejection fraction, hsTnT levels were detected in 98% of patients, and higher levels were predictive of cardiovascular death and heart failure (4).

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No studies have assessed change in troponin levels for prediction of outcomes in a broad population of patients with CHD who are clinically stable following myocardial infarction (MI) or unstable angina. We therefore measured troponin I (TnI) levels using a contemporary sensitive assay (5) at baseline and their change at 1 year in patients in the large LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease) study and evaluated their relationship to outcomes over long-term follow-up (6).

Methods

Study population. The design of the LIPID study has been described in detail previously (7). Patients 31 to 75 years of age, with an MI or hospital admission for unstable angina 3 to 36 months previously, entered the LIPID study if their plasma total cholesterol was 4.0 to 7.0 mmol/l (155 to 271 mg/dl) and fasting triglycerides <5.0 mmol/l (<445 mg/dl). Patients with heart failure were excluded. After an 8-week single-blind placebo run-in phase, 9,014 patients were randomly allocated to receive pravastatin 40 mg daily or matching placebo. Both groups continued to receive dietary advice. The median follow-up was 6 years. All deaths, MIs, and strokes were reviewed by blinded outcome assessment committees. MI was defined as definite development of new pathological Q waves of at least 0.03 s in at least 2 electrocardiogram leads or 2 of the following: 1) history of typical ischemic pain lasting for 15 min and unresponsive to sublingual nitrates; 2) elevation of creatine kinase-MB >2 times the upper limit of normal; and 3) evolution of ST-T changes.

Laboratory methods. Blood was drawn after a 12-h fast into EDTA tubes. Samples were stored in at least −70°C freezers until analysis. TnI was measured at randomization and at 1 year by the Siemens cTnI-Ultra assay (Erlangen, Germany), which is a contemporary sensitive assay (5). The assay has a limit of detection of 0.006 ng/ml, with a 99th percentile of 0.04 ng/ml for a normal reference population and a 10% coefficient of variation of 0.03 ng/ml (8) and 20% coefficient of variation of 0.17 ng/ml (9).

Statistical methods. All analyses were pre-specified in a biomarker protocol with the composite of CHD death and nonfatal MI (CHD events) as the primary endpoint. Other endpoints were expanded composites of major cardiovascular disease (CVD) events (CVD death, nonfatal MI, and stroke) and total CVD events (major CVD events, unstable angina, and revascularization), MI (both fatal and nonfatal), stroke, hospitalization for heart failure, coronary death, CVD death, and total mortality. It was pre-specified in our statistical analysis plan that all continuous variables were to be modeled using categories due to the skewed nature of most of these predictors. Estimated glomerular filtration rate and systolic blood pressure were analyzed in quartiles. Age was analyzed in 4 groups: <55, 55 to 64, 65 to 69, and ≥70 years. The data for TnI was split into approximate tertiles, with the cut points below the detection limit of 0.006 ng/ml (38%), 0.006 to <0.018 ng/ml (31%), and ≥0.018 ng/ml (31%). Change was defined as moving up or down one category. Change of ≥50% or <50% was also evaluated. Tests of trend over categories were performed using either logistic regression or ordinal logistic regression analyses as appropriate; for continuous data, the test for trend was performed using a linear model. The effects of pravastatin on change in TnI were examined with the Wilcoxon rank sum test.

The relationship between TnI and outcomes was assessed using a pre-specified time-to-event model adjusted for sex, treatment, prior stroke, diabetes mellitus, current smoking, hypertension, fasting glucose, total cholesterol, apolipoproteinB (ApoB), ApoA1, high-density lipoprotein cholesterol, triglycerides, age, nature of qualifying prior acute coronary syndromes (ACS), timing of coronary revascularization, systolic blood pressure, atrial fibrillation, estimated glomerular filtration rate, body mass index, dyspnea class, angina grade, white blood cell count, peripheral vascular disease, and use of aspirin at baseline. Each of these variables had been shown to be independent predictors of CVD events in risk models in the LIPID study (10–12). The relationship between change in TnI and subsequent events was assessed in a landmark analysis of 6,084 patients alive at 1 year who had not had an MI, stroke, revascularization, or unstable angina. An additional analysis including all patients regardless of revascularization, admission to hospital with unstable angina, or stroke was also performed. These analyses were adjusted for the above covariates as well as baseline TnI levels. A further analysis of main results was undertaken, with adjustment for 2 additional biomarkers separately: high-sensitivity C-reactive protein (hsCRP) and B-type natriuretic peptide (BNP).

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Discrimination of each risk model was assessed using the C-statistic, integrated discrimination index, and net reclassification improvement index (NRI). The NRI was calculated using event probabilities of ≤7.5%, 7.5% to 10%, >10% to 15%, and >15% for the primary outcome of CHD events. The LIPID study was a secondary prevention study and because there are no clinically meaningful categories published, we based our categories on pre-specified quartiles for CHD events. Because NRIs are not transferable from one setting to another, we have provided the relative NRIs of different factors in a multivariate model of interest. Patients changed classification if they moved between these categories in the 2 models with and without TnI. The base model included all risk factors stated earlier (including treatment), except for ApoA1 and ApoB. NRI was also calculated for change in TnI, when the base model included all risk factors in the previous model, as well as baseline TnI (13).

Results

Online Figure 1 shows the disposition of the patients. TnI was measured at baseline in 87% of patients. The patients who did not have TnI measurements were slightly younger and more likely to be smokers and not on aspirin. Otherwise, they were similar to those who had baseline biomarker measurements.

Baseline troponin levels. Table 1 shows the baseline characteristics of patients according to approximate tertiles of TnI. Patients in the highest tertiles of TnI levels were more likely to be older, have diabetes, have atrial fibrillation, have a history of hypertension or previous MI, and be taking angiotensin-converting enzyme inhibitors and were less likely to be on beta-blockers. Higher TnI levels were related to increased levels of BNP and hsCRP and increased LIPID risk score (10).

Baseline TnI levels were strongly related to the primary outcome of CHD event death ($p < 0.001$), as well as other CVD outcomes, including nonfatal MI, stroke, and heart failure. Following adjustment for 23 other baseline risk factors and treatment, TnI levels remained highly significant for these outcomes (all $p < 0.001$ except for stroke [$p = 0.02$]) and nonfatal MI ($p = 0.04$) (Fig. 1). In an additional analysis also adjusted for hsCRP and BNP levels, TnI independently predicted subsequent CHD events, major CVD events, total CVD events, MI, heart failure, and total mortality (Online Fig. 2).

Levels of TnI >0.04 ng/ml (99th percentile) were found in 8.4% of patients at baseline. Compared with undetectable levels, TnI levels >0.04 ng/ml were associated with an adjusted hazard ratio (HR) for CHD death or MI of 2.02 (95% CI: 1.66 to 2.45; p for trend < 0.001) and adjusted HR of 2.22 for all-cause mortality (95% CI: 1.81 to 2.72; p for trend <0.001).

Effect of pravastatin on troponin I levels. TnI levels were modestly lower at 1 year in patients randomized to receive pravastatin (median: 0.008 ng/ml [Q1 to Q3: 0.006 to 0.018]) versus baseline (median: 0.010 ng/ml [Q1 to Q3: 0.006 to 0.021]; $p < 0.001$). There was no change in the placebo group for TnI levels at 1 year (median: 0.009 ng/ml [Q1 to Q3: 0.006 to 0.019]) versus baseline 0.010 ng/ml (Q1 to Q3: 0.006 to 0.020; $p = 0.28$). This small treatment effect was statistically significant ($p = 0.002$) but did not result in important differences in the proportion of patients changing category (Tables 2 and 3).

The relative treatment effect of pravastatin was similar across each baseline category of TnI levels for CHD death and MI as well as other outcomes (Table 4). However, higher baseline TnI levels were associated with a larger absolute benefit of pravastatin and therefore fewer numbers needed to treat. For example, 37 patients would need to be treated with pravastatin over 5 years to prevent 1 additional CVD death for those with a TnI ≥0.018 ng/ml compared with 106 needed to treat for those with a TnI <0.006 ng/ml.

Overall change in troponin levels. Levels of TnI between baseline and 1 year decreased by one tertile category in 25.7%, increased in 23%, and were unchanged in 51.3% of patients and were not different by treatment (Table 2). The proportion of patients with a change in category was independent of randomized treatment (27% vs. 25% decreased category for pravastatin vs. placebo). Table 3 shows the percentage of patients changing categories from baseline to 1 year according to which categories they were in at baseline.

If TnI levels moved to a higher category, the adjusted HR for CHD events was 1.31 (95% CI: 1.06 to 1.62). The HR associated with a shift from nondetectable to the middle tertile compared with staying nondetectable was 1.34 (95% CI: 1.00 to 1.81), and the HR associated with a shift from the middle tertile to the highest tertile, compared with staying in the middle tertile, was 1.57 (95% CI: 1.15 to 2.14); however, if TnI levels decreased, the HR decreased (HR: 0.90; 95% CI: 0.74 to 1.09). The trend for a higher rate of events, if TnI levels increased, remained highly significant after adjustment for all other baseline variables, including baseline TnI category (p for trend = 0.01) (Fig. 2). An analysis containing both the baseline and 1-year TnI levels (rather than change) demonstrated that both were statistically significant in the model ($p < 0.001$ and $p = 0.01$, respectively).

In an analysis that included all patients between baseline and 1 year regardless of whether coronary revascularization, hospitalization for unstable angina, or stroke occurred, the results did not significantly change (Online Fig. 3).

Increases in TnI levels were associated with higher all-cause mortality (HR: 1.44; 95% CI: 1.16 to 1.79) and decreases in TnI were associated with a lower mortality (HR: 0.83; 95% CI: 0.68 to 1.02). Changes in TnI levels also significantly predicted the rate of major CVD events (increase HR: 1.33; decrease HR: 0.88), total CVD events (increase HR: 1.21; decrease HR: 0.89), CVD death (increase HR: 1.56; decrease HR: 0.77), and heart failure (increase HR: 1.49; decrease HR: 0.83) (all $p < 0.001$ except heart

Table 1 Baseline Characteristics

	Troponin < Detectable Range <0.006 ng/ml (n = 2,967)	Troponin 0.006–<0.018 ng/ml (n = 2,436)	Troponin ≥0.018 ng/ml (n = 2,460)	p Trend
Randomized to pravastatin	1,486 (50)	1,211 (50)	1,244 (51)	0.66
Troponin, ng/ml	0.006 ± 0.000	0.012 ± 0.003	0.048 ± 0.097	<0.001
Age at randomization, yrs	61.0 (54.0–67.0)	62.0 (56.0–68.0)	64.0 (57.0–68.0)	<0.001
Age ≥65 yrs	1,030 (35)	972 (40)	1,107 (45)	<0.001
Female	538 (18)	407 (17)	388 (16)	0.03
Months from QE	14.5 (8.1–25.6)	13.9 (7.8–25.2)	13.3 (7.7–24.3)	<0.01
Current smoker	285 (10)	218 (9)	232 (9)	0.96
Hypertension	1,159 (39)	1,054 (43)	1,078 (44)	<0.01
Diabetes	229 (8)	200 (8)	247 (10)	<0.01
Obese	521 (18)	412 (17)	464 (19)	0.14
Previous stroke	97 (3)	95 (4)	130 (5)	<0.001
Systolic BP, mm Hg	133 ± 19	135 ± 20	135 ± 20	0.02
Diastolic BP, mm Hg	80 ± 11	81 ± 11	80 ± 11	0.68
Dyspnea NYHA class >I	266 (9)	217 (9)	278 (11)	<0.01
Angina CCVS grade >0	1,123 (38)	880 (36)	924 (38)	0.96
Atrial fibrillation	25 (1)	38 (2)	47 (2)	<0.01
Total cholesterol, mmol/l	5.6 ± 0.8	5.7 ± 0.8	5.7 ± 0.8	<0.001
LDL cholesterol, mmol/l	3.9 ± 0.7	3.9 ± 0.7	3.9 ± 0.7	<0.001
HDL cholesterol, mmol/l	0.9 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	<0.001
Triglycerides, mmol/l	1.5 (1.2–2.1)	1.6 (1.2–2.2)	1.6 (1.2–2.2)	<0.01
Total cholesterol:HDL cholesterol	6.2 ± 1.5	6.2 ± 1.5	6.2 ± 1.6	0.75
eGFR, ml/min/1.73 m^2	71 (61–82)	70 (61–80)	68 (58–78)	<0.001
WBC count, × 10^8	6.9 (5.9–8.1)	7.0 (6.0–8.2)	7.1 (6.1–8.3)	<0.001
Previous coronary revascularization				
No revascularization	1,706 (57)	1,466 (60)	1,438 (58)	0.78
PCI only	379 (13)	260 (11)	231 (9)	
CABG only	776 (26)	644 (26)	721 (29)	
PCI and CABG	106 (4)	66 (3)	70 (3)	
No MI	1,256 (42)	851 (35)	736 (30)	<0.001
Single MI	1,459 (49)	1,305 (54)	1,351 (55)	
Multiple MIs	252 (8)	280 (11)	373 (15)	
Medications				
Aspirin	2,469 (83)	2,020 (83)	2,012 (82)	0.15
ACE inhibitors	331 (11)	384 (16)	539 (22)	<0.001
Beta-blockers	1,418 (48)	1,199 (49)	1,074 (44)	<0.001
Calcium antagonists	1,048 (35)	803 (33)	837 (34)	0.50
LIPID risk score (8)	5.4 ± 3.3	5.9 ± 3.5	6.3 ± 3.7	<0.001
Baseline biomarker levels				
BNP, pg/ml	18.6 (7.9–37.3)	23.3 (9.7–51.1)	31.7 (13.1–71.2)	<0.001
hsCRP, mg/l	2.3 (1.2–4.6)	2.4 (1.2–4.6)	2.7 (1.3–5.2)	0.13

Values are n (%), mean ± SD, or median (interquartile range).

ACE = angiotensin-converting enzyme; BNP = B-type natriuretic peptide; BP = blood pressure; CABG = coronary artery bypass graft; CCVS = Canadian Cardiovascular Society; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; IQR = interquartile range; LDL = low-density-lipoprotein; LIPID = Long-Term Intervention With Pravastatin in Ischaemic Disease; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; QE = qualifying event; WBC = white blood cell.

failure [p = 0.002]). Changes in TnI levels were not so significantly associated with MI or stroke (p = 0.07).

The effect of pravastatin on CVD event reduction remained essentially unchanged after adjustment for change in TnI levels. For example, pravastatin reduced the number of CHD events by 24% (HR: 0.76; p < 0.001), major CVD events by 25% (HR: 0.75; p < 0.001), total CVD events by 21% (HR: 0.79; p < 0.001), and all-cause mortality by 25% (HR: 0.75; p < 0.001) after adjustment for baseline risk factors, baseline TnI levels, and change in baseline TnI category.

On multivariate analysis, with the addition of baseline hsCRP and change, change in TnI level remained an independent predictor for all of the above mentioned outcomes (each p < 0.003 except for CHD events [p = 0.02]). When baseline BNP and change were added to the 23 baseline risk factors, change in TnI level remained significant for all endpoints (p < 0.008) except for CHD events (p = 0.05).

Findings were similar when a 50% change was used rather than tertile category as the criterion for change except

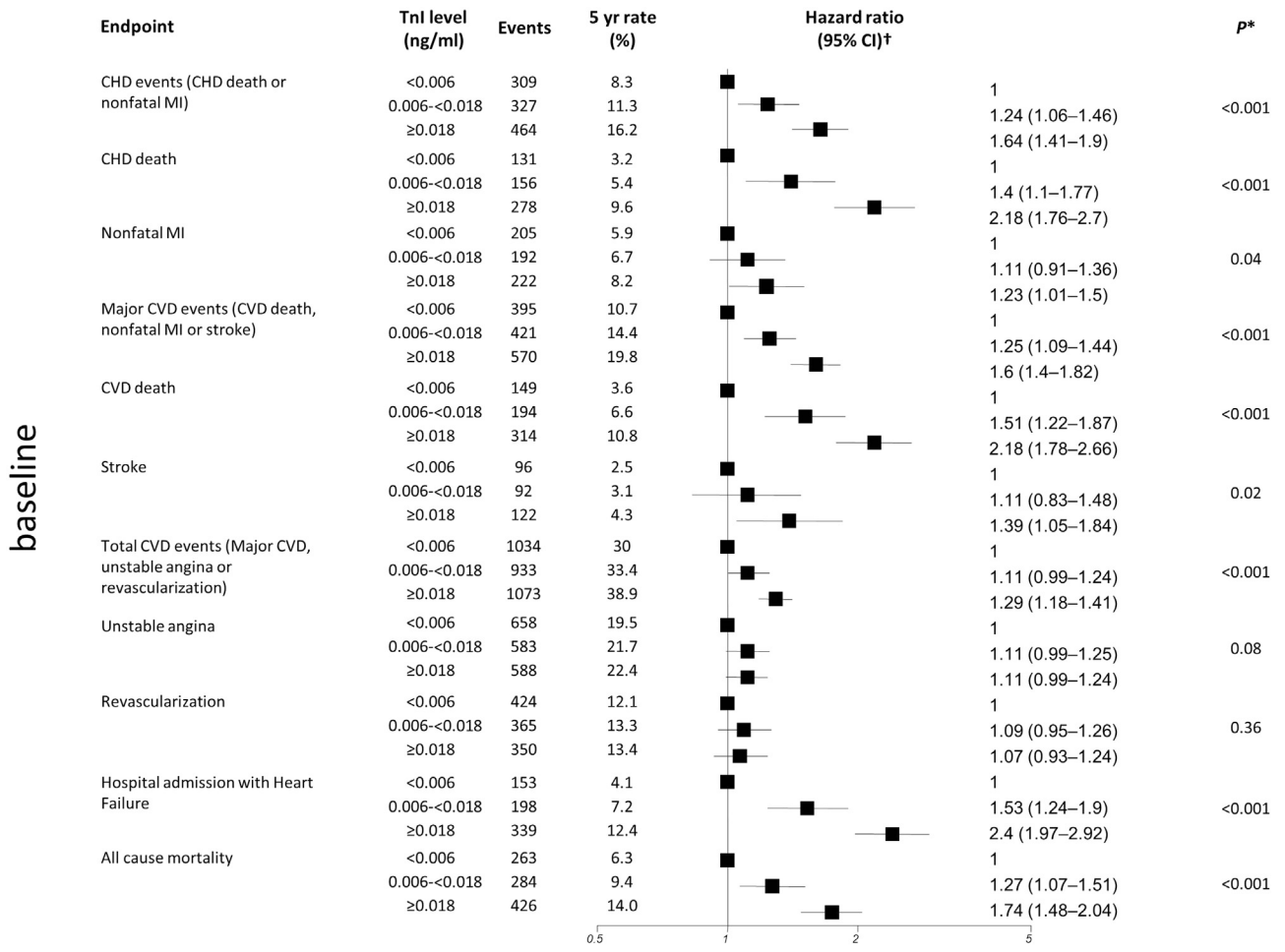

Figure 1 **Forest Plots Showing Outcomes Related to Baseline Troponin I Levels Adjusted for 23 Baseline Variables and Treatment**

Hazard ratios (HRs) were compared with not detectable troponin I (TnI) group. *p value for trend. †HRs and 95% CI were adjusted for baseline variables: treatment, sex, stroke, diabetes, smoking, hypertension, total cholesterol, apolipoprotein B (ApoB), ApoA1, high-density lipoprotein cholesterol, age, nature of prior acute coronary syndrome, timing of coronary revascularization, systolic blood pressure, atrial fibrillation, estimated glomerular filtration rate, body mass index, dyspnea class, angina grade, white blood cell count, peripheral vascular disease, triglycerides, fasting glucose, and aspirin at baseline. CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction.

that to change independently predicted stroke (p = 0.02) (Fig. 3). No factors were identified that predicted either an increase or decrease in TnI levels. Online Figure 4 shows the results for a 50% change for all patients, including those who had an event between baseline and 1 year. No factors were identified that predicted either an increase or decrease in TnI levels.

NRI, C-statistic, and integrated discrimination index. Table 5 shows the baseline and landmark reclassifications for CHD death and MI and for mortality. For mortality, the baseline model improved classification by 4.8% and the landmark model by 1.4% with the C-statistic changing from 0.665 to 0.673 for the baseline model and from 0.675 to 0.677 for the landmark model.

Table 2 **Change in Troponin I Levels From Baseline to Year 1***

	Placebo (n = 3,036)	Pravastatin (n = 3,048)
Lower	750 (24.7%)	815 (26.7%)
Same	1,564 (51.5%)	1,556 (51.1%)
Higher	722 (23.8%)	677 (22.2%)

Values are n (%). *p = 0.19: changes are recorded as either in the same category (not detectable, 0.006 to <0.018, or ≥0.018) or in a lower or higher category compared with baseline.

Table 3 **Overall Change in Troponin I Levels From Baseline to Year 1**

	Troponin Levels at Year 1		
	Not Detectable	0.006–<0.018 ng/ml	≥0.018 ng/ml
Not detectable	62.1%	23.8%	14.1%
0.006–<0.018 ng/ml	35.3%	36.3%	28.4%
≥0.018 ng/ml	20.0%	27.5%	52.5%

Table 4 Effect of Pravastatin Treatment on Clinical Events by Baseline Troponin I Category

Endpoint	TnI Level, ng/ml	Placebo, 5-yr rate %	Pravastatin, 5-yr rate %	Hazard Ratio (95% CI)*	NNT
CHD events (CHD death or nonfatal MI)	<0.006	9.3	7.3	0.73 (0.58–0.92)	52
	0.006–<0.018	12.6	10.0	0.75 (0.60–0.93)	39
	≥0.018	17.4	15.1	0.85 (0.71–1.02)	29
Major CVD events (CVD death, nonfatal MI, or stroke)	<0.006	12.1	9.3	0.74 (0.61–0.90)	39
	0.006–<0.018	15.7	13.0	0.77 (0.63–0.93)	31
	≥0.018	21.7	18.0	0.81 (0.69–0.95)	23
Total CVD events (major CVD, unstable angina, or revascularization)	<0.006	31.6	28.4	0.87 (0.77–0.98)	26
	0.006–<0.018	35.5	31.3	0.85 (0.75–0.97)	24
	≥0.018	41.4	36.4	0.83 (0.74–0.94)	21
CVD death	<0.006	4.0	3.3	0.72 (0.52–0.99)	106
	0.006–<0.018	7.5	5.7	0.70 (0.53–0.93)	58
	≥0.018	11.9	9.7	0.81 (0.65–1.02)	37
All-cause mortality	<0.006	6.9	5.7	0.74 (0.58–0.94)	63
	0.006–<0.018	10.6	8.1	0.68 (0.54–0.86)	42
	≥0.018	14.7	13.2	0.84 (0.69–1.01)	31

*Test for interaction not significant for any category. Hazard ratios and 95% CI were adjusted for baseline troponin I (TnI) levels and for treatment, sex, stroke, diabetes, smoking, hypertension, total cholesterol, apolipoprotein B, apolipoprotein A1, HDL cholesterol, age, nature of prior acute coronary syndromes, timing of coronary revascularization, systolic BP, atrial fibrillation, eGFR, body mass index, dyspnea class, angina grade, WBC count, peripheral vascular disease, triglycerides, fasting glucose, and aspirin at baseline.

CHD = coronary heart disease; CVD = cardiovascular disease; NNT = number needed to treat; other abbreviations as in Table 1.

The NRI with TnI was the second largest, before age and after history of MI (Online Table 1).

Discussion

This study shows that baseline TnI levels measured with a contemporary sensitive assay (5,14) are predictive of the pre-specified combined endpoint of CHD death and MI (highest tertile compared with lowest 64%) in patients who were stable following a previous MI or unstable angina.

The contemporary sensitive TnI used in this study has a coefficient variation of 10% <99th percentile and has been reported to detect troponin levels in 46.6% of a healthy population (15). In the current study, levels of TnI were detected in 62.3% of patients. Baseline TnI levels were also predictive of an increase in a number of other events, including MI (23% increase), stroke (39% increase), heart failure (240% increase), and all-cause mortality (74% increase). The effect of elevated baseline TnI levels appeared to be greater on fatal than nonfatal CVD events.

Another novel finding was that changes in levels over the first year were predictors of CHD death and MI. Changes were also related to all-cause mortality, with increased levels being associated with increased mortality and decreases being associated with decreased mortality.

The small effect of pravastatin on troponin levels was statistically significant but not clinically important.

Baseline troponin levels. The reasons for baseline troponin elevations in patients with stable CHD may be multiple (16), including subclinical ischemia, left ventricular hypertrophy (LVH) (17,18), hypertension, diabetes (19), atrial fibrillation (20), or plaque rupture and microemboli causing myocyte necrosis. Troponin levels may increase with ischemia alone (16,21). It is therefore possible that the elevations of TnI levels may have been related to episodes of repetitive ischemia.

Several studies have shown an association between hsTnT levels and computed tomography angiography or invasive angiographic severity of coronary artery disease in patients with stable CHD (22,23). However, in one study, there was no correlation with levels of hsTnT and extent of angiographic disease, but there was a correlation with calcium scoring and with the composition of coronary plaques as assessed by computed tomography angiography (24). In another study, patients with higher levels of hsTnT had more noncalcified coronary lesions, higher plaque volume, and positively remodeled plaques, all features that have been shown to correlate with risk of ACS (25,26).

It is well known that coronary artery plaque ruptures occur frequently and that most are silent (27). Therefore, the occurrence of plaque rupture and microemboli causing myocyte necrosis may explain increased levels of troponin in some patients at baseline and the association with nonfatal MI.

However, our finding that the association of TnI levels with nonfatal MI was weaker than for heart failure suggests that the association may be more related to structural heart disease than plaque rupture. This is supported by the PEACE (Prevention of Events With Angiotensin Converting Enzyme Inhibition) trial in patients with stable CHD (55% of whom had previous MI) and normal systolic function, in which elevated levels of hsTnT (>1 ng/l) had a strong and graded association with the risk of both CVD and heart failure but not MI (4).

Changes in troponin levels. TnI levels changed in approximately 50% of patients over 1 year. Changes in TnI moving from one tertile to another were related to increases in the number of events, including hospitalization for heart

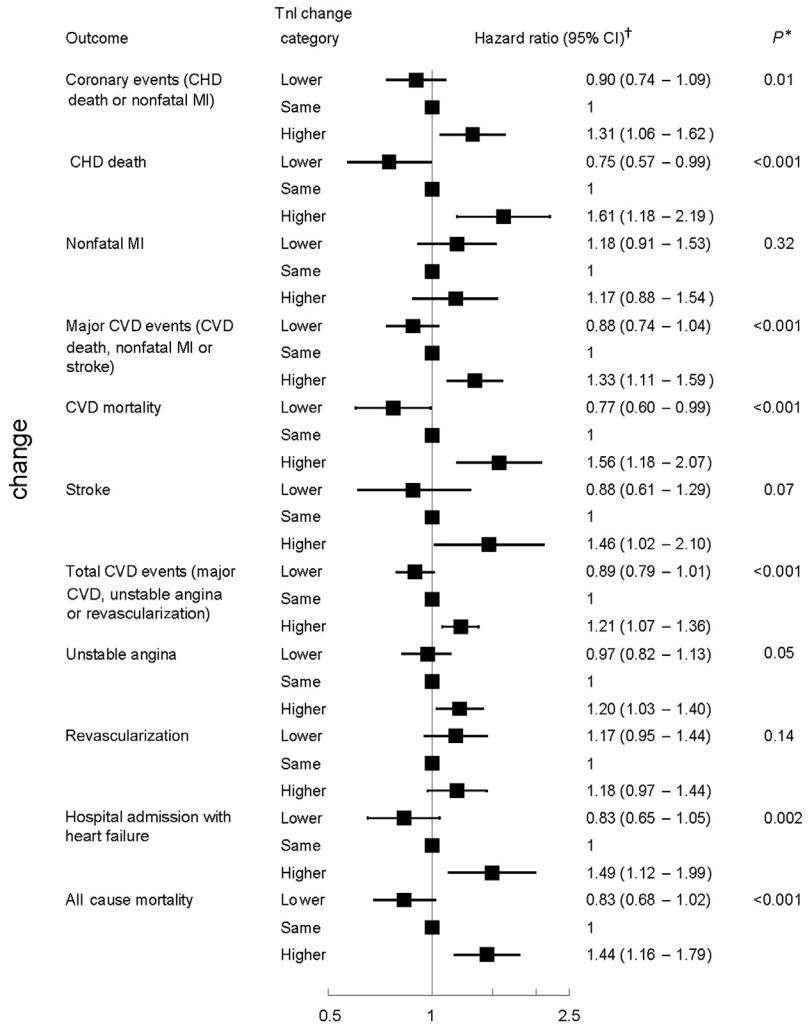

Figure 2 **Forest Plots Showing Outcomes Related to Change in Troponin Levels According to Tertile Increase or Decrease, Adjusted for 23 Baseline Variables and Baseline Troponin Tertile Category**

HRs were compared with no change in TnI groups. *p value for trend. †HRs and 95% CI were adjusted for baseline TnI levels and for treatment, sex, stroke, diabetes, smoking, hypertension, total cholesterol, ApoB, ApoA1, high-density lipoprotein cholesterol, age, nature of prior acute coronary syndrome, timing of coronary revascularization, systolic blood pressure, atrial fibrillation, estimated glomerular filtration rate, body mass index, dyspnea class, angina grade, white blood cell count, peripheral vascular disease, triglycerides, fasting glucose, and aspirin at baseline. Abbreviations as in Figure 1.

failure, unstable angina, coronary revascularization, and mortality. For nonfatal MI, both decreases and increases in TnI levels were associated with higher HRs and the p value for trend was nonsignificant ($p = 0.32$). The findings were similar with change criteria of 50%.

Previous studies have reported an association between increases in troponin levels and adverse outcomes in patients with chest pain (28), with heart failure (29) and in an elderly community population (3). Several studies have also reported that decreases in troponin levels are associated with decreases in number of events (3,30,31).

Our findings of changes in troponin levels over 1 year have plausible potential explanations. Increases in troponin levels over time could relate to ongoing myocyte necrosis related to the original MI; however, this is unlikely because patients were enrolled for a minimum of 3 months to 3 years after the index event and increases in troponin levels are more likely due to chronic processes related to LVH (17,18), increasing renal dysfunction, exacerbation of airway disease (31), or poor diabetes control (19). Increases in troponin levels could also relate to new events such as the development of atrial fibrillation (20), or plaque rupture, which is supported by our findings of an association with unstable angina and revascularization but not with our finding of no association with MI.

Decreases in troponin levels could relate to decreases in LVH related to better hypertension treatment, improvement in renal function or diabetes control, or other risk factor

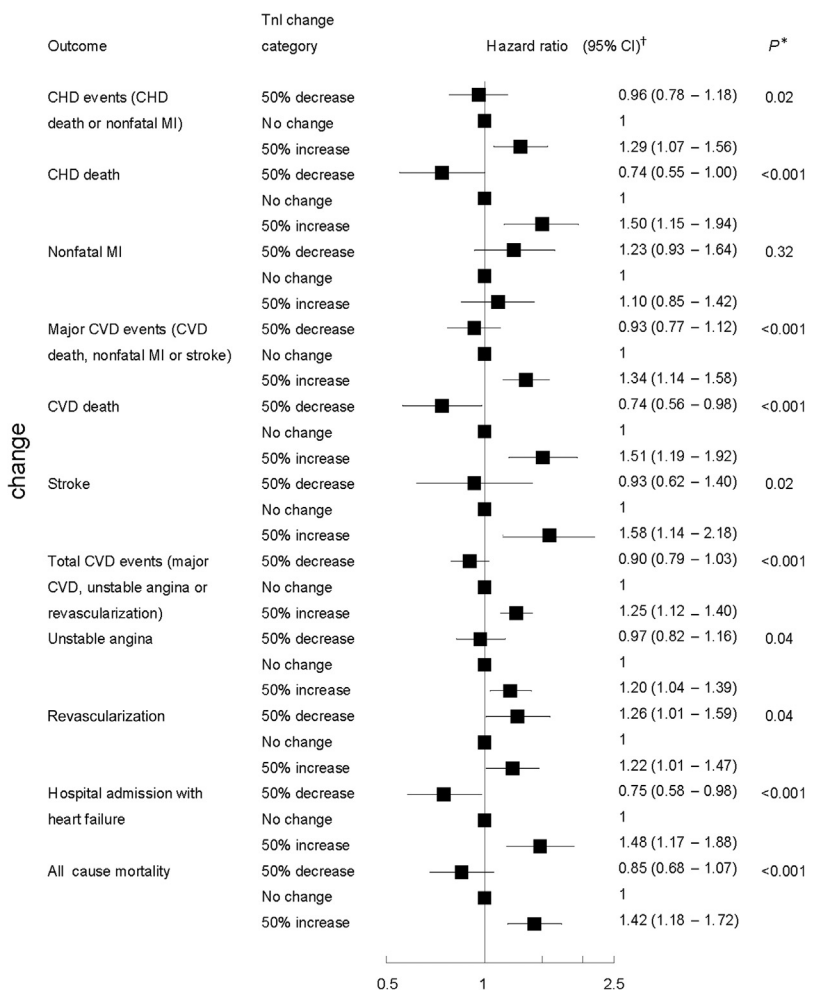

Figure 3 Landmark Models With 50% Change Criteria

*p value for trend. †HRs and 95% CI were adjusted for baseline TnI levels and for treatment, sex, stroke, diabetes, smoking, hypertension, total cholesterol, ApoB, ApoA1, high-density lipoprotein cholesterol, age, nature of prior acute coronary syndrome, timing of coronary revascularization, systolic blood pressure, atrial fibrillation, estimated glomerular filtration rate, body mass index, dyspnea class, angina grade, white blood cell count, peripheral vascular disease, triglycerides, fasting glucose, and aspirin at baseline. Abbreviations as in Figure 1.

influences (e.g., cessation of smoking) (4). Although some changes in TnI levels may alter subsequent risk through such mechanisms, these changes were not related to the effects of pravastatin in lowering the number of CHD events.

Overall, troponin levels may identify patients at high global cardiovascular risk because baseline levels predicted CHD death, MI, heart failure, stroke, and total mortality. Changes in troponin levels modified risk for these events and were modestly associated with admission with unstable angina and revascularization. It may be possible to tailor therapy according to risk on the basis of troponin levels (e.g., intensive risk factor modification).

Relationship with stroke. In the current study in patients with stable CHD who were predominantly in sinus rhythm, both baseline and changes in TnI levels were associated with risk of stroke ($p = 0.07$ using categories and $p = 0.02$ using 50% change criteria). This is consistent with the finding in patients in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study (20) with atrial fibrillation that higher levels of TnI were associated with higher rates of stroke.

Net reclassification improvement. Adding TnI to the baseline risk model resulted in a modest improvement in the NRI of 4.8%. Although the change in NRI appears small, it was larger than that for age. Also, TnI levels added to the LIPID risk model remained an independent predictor of CHD death and MI after the addition of BNP and hsCRP. This suggests that these biomarkers are related to different mechanisms and carry different prognostic information in stable patients after MI or unstable angina. Furthermore, TnI level remained statistically significant for a range of clinical outcomes. This illustrates that TnI is important in

Table 5 Baseline and Landmark NRI, C-Statistic, and IDI for the Endpoint of CHD Death and MI

	NRI		IDI		C-statistic	
	NRI, %	p Value	IDI	p Value	Without Troponin	With Troponin
Baseline						
Troponin added	4.76	0.01	0.0035	<0.001	0.665	0.673
Landmark						
Troponin added	1.38	0.48	0.0009	0.04	0.675	0.677

Based on the same endpoint probabilities: ≤7.5%, 7.5% to 10%, 10% to ≤15%, and >15%. Patients changed classification if they moved between these categories in these 2 models (with and without troponin). The model without troponin included treatment, sex, stroke, diabetes, smoking, hypertension, total cholesterol, HDL cholesterol, age, nature of prior acute coronary syndrome, timing of coronary revascularization, systolic BP, atrial fibrillation, eGFR, body mass index, dyspnea class, angina grade, WBC count, peripheral vascular disease, triglycerides, fasting glucose, and aspirin at baseline. For the landmark model, it also included baseline troponin level.

IDI = integrated discrimination index; NRI = net reclassification involvement index; other abbreviation as in Tables 1, 2, and 3.

the pathophysiology and natural history of patients with CHD.

Study limitations. Biomarkers were not measured in all patients. Choice of approximate tertiles was pragmatic and driven largely by the fact that one-third of values were not detectable (<0.006) using this TnI assay. Two-thirds of the troponin values analyzed (and the entire middle tertile) were below the level of guideline-endorsed analytical precision for this assay (8). However, any analytical noise because of imprecision in that range would be expected to have weakened the observed risk relationships (15). The categories used in the NRI are new because this was a secondary prevention population at higher risk of events.

The biological variability and analytical variation of the contemporary sensitive TnI assay we used may have influenced the findings related to change in TnI levels over 1 year. Also, it is possible that regression to the mean may have affected changes in measurements over time. We prespecified the change criterion on the basis of tertiles. Our findings were similar using 50% increase or decrease criteria which would be expected to be greater than the biological variability (8). We used a World Health Organization protocol definition for MI and not the universal definition (32), which would have detected many more MIs. In our multivariate analysis, we did not have sufficient data to include ejection fraction.

The LIPID study was conducted some years ago. However, the cohort has ongoing major relevance to current clinical management. The study was undertaken in patients who were at least 3 months after their qualifying MI or hospitalization for unstable angina. Therefore, subsequent major developments in the acute management of ACS are not pertinent. Indeed, there was very high background usage of present evidence-based therapies for ongoing prevention in randomized patients. Furthermore, patients had a broad range of cholesterol levels, reflecting those in usual clinical practice. The cohort is one of the most well characterized in research trials in CHD. Vital status was ascertained in all but 1 patient, and all major cardiovascular events, the endpoints in the present study, were adjudicated.

Conclusions

Baseline TnI levels were independent predictors of CHD death and nonfatal MI, as well as mortality and a wide range of other CVD events, including heart failure and stroke. Increases in TnI levels from baseline to 1 year were associated with higher total mortality, and decreases were associated with decreased total mortality.

Pravastatin resulted in a slightly greater reduction in TnI levels than placebo but did not account for any of the effects of pravastatin in reducing the number of CVD events. Further research is needed to determine whether measurement of baseline levels and change in TnI could guide therapy, for example, by prompting more intensive risk factor modification.

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Key Words: coronary heart disease ■ LIPID ■ mortality ■ troponin I.

APPENDIX

For supplemental figures and a table, please see the online version of this article.